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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/484,895	01/18/2000	John J. Harrington	5817-7G	1246

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/484,895	Applicant(s) HARRINGTON ET AL.	
	Examiner Quang Nguyen	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58,61-109 and 113-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58,61-109 and 113-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed March 01, 2002 in Paper No. 12 has been entered.

Claims 58, 61-109 and 113-118 are pending in the present application.

Following is a new ground of rejection.

Claim Rejections - 35 USC § 112

Claims 70-96, 106-107, 113-116 and 118 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(i) A vector construct comprising: (a) a first promoter operably linked to a positive selectable marker encoding DNA sequence, (b) a second promoter operably linked to a negative selectable marker encoding DNA sequence, and (c) an unpaired splice donor site, wherein said unpaired splice donor site is located 5' upstream of said negative selectable marker encoding DNA sequence, and wherein said positive and negative selectable marker sequences and said splice donor site are oriented in an orientation whereby when said vector construct is integrated into a genome of a eukaryotic host cell and the vector-encoded splice donor site is spliced to a splice acceptor in an endogenous gene in said genome, then said positive selectable marker is expressed in active form and said negative selectable marker sequence is not expressed;

(ii) an isolated eukaryotic host cell, a library of eukaryotic cells comprising the above vector construct or any of the vectors of claims 58, 65 and 67; and *in vitro* methods for activation of an endogenous gene, for obtaining cDNA from an endogenous

gene, for producing a protein using the vector of any one of claims 58, 61, 65 and 67 in a vector-genomic DNA complex in a suitable eukaryotic cell *in vitro*;

does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 70-78, 113-116 and 118 are drawn to a vector construct of claim 70 having the limitations recited in the claims. Claims 79-92 are directed to a host cell *in vitro* and a library of cells *in vitro* comprising any one of the vectors of the presently claimed invention. Claims 93-96 are drawn to methods for activation of an endogenous gene in a cell *in vitro* and for obtaining cDNA from an endogenous gene in a cell using the vector of any one of claims 58, 65, 67, 70 or 71. Claims 106-107 are directed to a method for producing a protein using the vector of any one of claims 58, 61, 65 or 67 in a vector-genomic DNA complex in any suitable cells *in vitro*.

The specification is not enabled for the instant broadly claimed invention for the reasons discussed below.

With respect to claims 70-78, 113-116 and 118, the claims encompass any structural orientations for the combination of a first promoter, a second promoter and an unpaired splice donor site in the vector to attain the functional limitation recited in claim 70. Apart from the scope given to this vector, the instant specification fails to provide sufficient guidance on at least a representative number of structural arrangements for the recited components to meet the functional limitation to reflect the breadth of the

instant claims. The present disclosure also fails to teach how to use a vector construct wherein the negative selectable marker has been made inactive via the introduction of a splice donor site in its encoded sequence. This is because it is irrelevant whether the vector is integrated and properly spliced into the genome of a eukaryotic vector, because the negative selectable marker has been purposely inactivated. It should be noted that the scope of claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill. As such, with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to use the full scope of the vector as claimed, as well as a host cell, a library of cells and methods of using the same.

The instant claims encompass any host cell, a library of any cell, and methods for activation of an endogenous gene in any cell *in vitro*, for obtaining cDNA from an endogenous gene in any cell, and for producing a protein in any cell using any one of the vectors of the presently claimed invention. The claims encompass non-eukaryotic cells such as prokaryotes or bacteria cells. However, apart from the teachings of making and using the vectors of the presently claimed invention for non-targeted activation of endogenous genes in eukaryotic cells, the instant specification offers no guidance for a skilled artisan on how to make and use of the same in any non-eukaryotic cells. Moreover, it is well known in the art that unlike eukaryotes, in prokaryotes a polypeptide chain is generally encoded by a DNA sequence that is co-linear with the amino acid sequence (page 867, first paragraph, In Principles of Biochemistry (Lehninger et al., eds.), Second Edition, 1997) indicating that prokaryotes

may not have the necessary components for mediating splicing of mRNA molecules. As such, then how would any of the vector of the presently claimed invention activate endogenous genes or genomic DNA contained in the vector genomic DNA complex in bacteria or prokaryotes. Therefore, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention.

Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

Applicants' arguments related to the new rejection above in the Amendment filed on March 01, 2002 in Paper No. 12 (pages 24-26) have been fully considered.

Applicants mainly argued that a person of ordinary skill artisan would have known how the recited component function and therefore would have known how to

arrange them to meet the claimed functional limitation. Applicants further directed examiner to Appendix A labeled "Claim 70" to demonstrate how the claimed vector could be used to produce the products in the diagram.

Applicants' arguments are respectfully found unpersuasive because neither the specification nor the Appendix A shows any other structural arrangements for the claimed vector apart from one wherein the unpaired splice donor site is located 5' upstream of the negative selectable marker encoding DNA sequence to meet the functional limitation of the claims. Since this is the essential feature of the claimed vector, it must be recited in the claims.

Accordingly, the claims are rejected for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 70-100, 102-105, 108-109 and 113-118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 96, the phrase "said isolation is accomplished by sequencing" is unclear. It should be noted that sequencing is not an isolating step. The cDNA must be isolated somehow prior to be sequenced. The metes and bounds of the claim are not clearly determined.

Regarding claims 70, 97, 117-118 and the dependent claims, the phrase "such that" renders the claims indefinite because it is unclear whether the limitations following

the phrase are part of the claimed invention. See MPEP § 2173.05(d). As such, the metes and bounds of the claims are not clearly determined.

In claim 100, "using" is not an active step for the claimed method, therefore the metes and bounds of the claim can not be clearly determined. Which active steps are involved in using the endogenous gene sequence to recover exon I of the endogenous gene?

In claims 102, 103 and dependent claims 104-105, 108-109, the phrase "one or more genes encoded by said vector" in step (d) is unclear. This is because apart from inserting an isolated genomic DNA sequence into any of the recited vectors, the vectors do not contain one or more genes for transcription in step (d). For example, in a vector-genomic DNA complex, genes from the genomic DNA complex would be transcribed, not those encoded by the vector.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 58, 61-109 and 113-118 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-58 of U.S. Patent No. 6,361,972. Although the conflicting claims are not identical, they are not patentably distinct from each other because the vectors, a host cell or a library of cells containing the same and methods of using the same of the instant application encompass embodiments of the vectors, eukaryotic cells, libraries of cells and methods of use in the issued U.S. Patent No. 6,361,972.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER